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(57) Abstract

Substituted 4,5-diaryl heterocycles, processes for preparing them, pharmaceutical compositions containing them and their use in therapy, inter alia, in the treatment of cardiovascular disorders.

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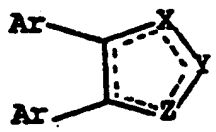
COMPOUNDS

The present invention relates to novel substituted heterocyclic compounds, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

The present invention therefore provides in a first aspect compounds of structure (I):



(I)

in which

each group Ar is the same or different and is optionally substituted phenyl or optionally substituted heteroaryl;

X is nitrogen or CR^1

Y is nitrogen, $N(CH_2)_nA$ or $C(CH_2)_nA$

Z is nitrogen, oxygen or $N(CH_2)_nA$, and the dotted line indicates the optional presence of a double bond so as to form a fully unsaturated heterocyclic ring;

R^1 is hydrogen, C_{1-4}alkyl, optionally substituted phenyl or optionally substituted heteroaryl;

n is 4 to 12; and

A is CO_2H or a group hydrolysable to CO_2H, 5-tetrazolyl, SO_3H, $P(O)(OR)_2$, $P(O)(OH)_2$, or $P(O)(R)(OR)$ in which R is hydrogen or C_{1-4}alkyl, or a pharmaceutically acceptable salt thereof, provided that

- X, Y and Z are not all at the same time, nitrogen;

- when X is CR^1, Y and Z are not both nitrogen;
- when Y is $N(CH_2)_nA$, Z is nitrogen; and
- when Z is oxygen, Y is $C(CH_2)_nA$.

Suitably, each group Ar is the same and is optionally substituted phenyl or optionally substituted heteroaryl. More suitably, each group Ar is the same and is optionally substituted phenyl. Preferably each group Ar is the same and is unsubstituted phenyl.

Suitably, X is nitrogen or CR^1; preferably X is nitrogen.

Suitably, Y is nitrogen, $N(CH_2)_nA$ or $C(CH_2)_nA$; preferably, Y is nitrogen or $N(CH_2)_nA$; most preferably Y is $N(CH_2)_nA$.

Suitably, Z is nitrogen, $N(CH_2)_nA$ or oxygen; preferably Z is nitrogen or $N(CH_2)_nA$; most preferably Z is nitrogen.

Suitably, n is 4 to 12, preferably 4 to 8 and most preferably 7 or 8.

Suitably, A is CO_2H or a group hydrolysable to CO_2H, 5-tetrazolyl, SO_3H, $P(O)(OR)_2$, $P(O)(OH)_2$, or $P(O)(R)(OR)$ in which R is hydrogen or C_{1-4}alkyl; preferably A is CO_2H or a group hydrolysable to CO_2H, for example CO_2C_{1-4}alkyl such as CO_2CH_3 or $CO_2C_2H_5$.

Suitably, R^1 is hydrogen, C_{1-4}alkyl, optionally substituted phenyl or optionally substituted heteroaryl. Preferably R^1 is hydrogen.

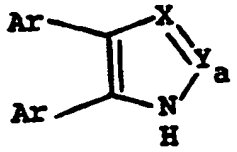
Suitable substituents for phenyl groups Ar and R^1 include, for example, 1-3 groups which may be the same or different and are selected from C_{1-4}alkyl, haloC_{1-4}alkyl such as CF_3, halogen, hydroxy and C_{1-4}alkoxy.

Suitable heteroaryl groups include, for example, saturated or unsaturated 5- or 6-membered rings comprising 1 to 3 heteroatoms selected from nitrogen, oxygen and sulphur. Preferred such rings include, for example, thienyl and furyl rings.

Particularly preferred compounds of structure (I) include:
2-(8-carboxyoctyl)-4,5-diphenyltriazole;
1-(8-carboxyoctyl)-4,5-diphenyltriazole; and
2-(8-ethoxycarbonyloctyl)-4,5-diphenyltriazole.

The compounds of structure (I) can be prepared using procedures analogous to those known in the art. The present invention therefore provides in a further aspect a process for the preparation of compounds of structure (I) which comprises:

(a) for compounds in which Z is other than oxygen reaction of a compound of structure (II):



(II)

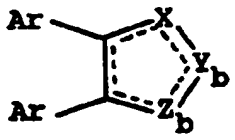
in which
Ar and X are as described in structure (I) and Y_a is N

or $C(CH_2)_nA$; with a compound of structure:

$$L(CH_2)_nA \qquad (III)$$

in which n and A are as described for structure (I) and L is a leaving group; or

(b) reaction of a compound of structure (IV):



(IV)

in which Ar and X are as described in structure (I), Y_b is N, $N(CH_2)_nA_b$ or $C(CH_2)_nA_b$, Z_b is N, O or $N(CH_2)_nA_b$ provided that:

- X, Y_b and Z_b are not all nitrogen,
- when X is CR^1, Y_b and Z_b are not both nitrogen,
- when Y_b is $N(CH_2)_nA_b$, Z_b is nitrogen, and
- when Z_b is O, Y_b is $-C(CH_2)_nA_b$;

A_b is a group convertible to a group A as described in structure (I), with a reagent suitable to convert the group A_b into a group A and, optionally thereafter, converting one group A into another group A, and optionally forming a salt.

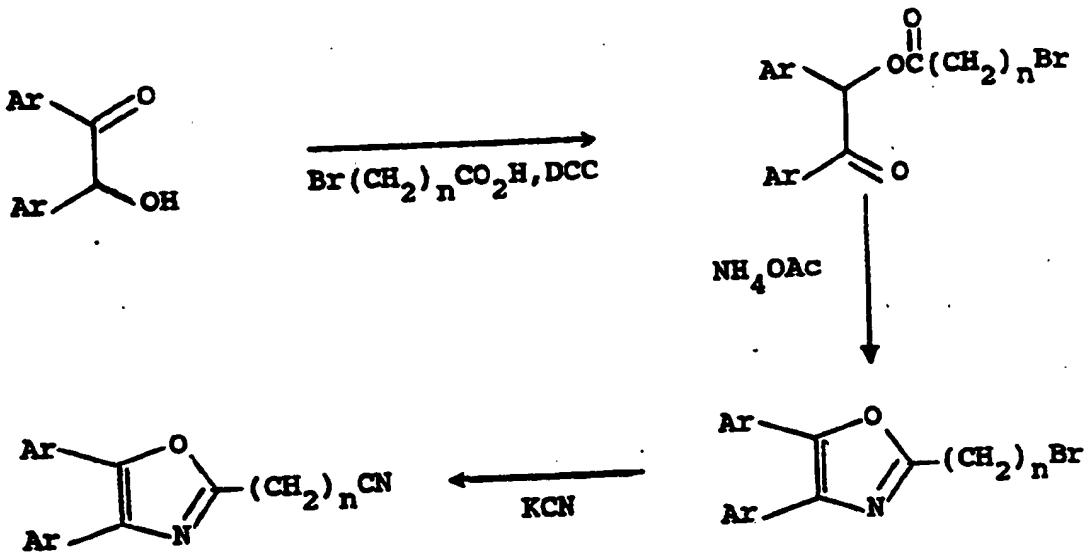
Suitable leaving groups L will be apparent to those skilled in the art and include, for example, halogen, such as bromine.

Suitable groups A_b convertible to a group A include, for example, where A is CO_2H, CN groups, which

can be converted into CO_2H groups by reaction with, for example, sulphuric acid. Other groups and suitable reagents will be apparent to those skilled in the art.

The reaction between compounds of structures (II) and (III) can be carried out in a suitable solvent in the presence of a base at a temperature of between ambient and the reflux temperature of the solvent used. For example, compounds of structure (I) in which X and Y are both nitrogen and Z is $N(CH_2)_nCO_2R$, can be prepared by reacting a compound of structure (II) in which X and Y_a are both nitrogen with a compound of structure (III) in which L is bromine and A is CO_2H, in aqueous solution in the presence of sodium hydroxide as base. Further reaction of said compound of structure (I) with, for example, p-toluene sulphonic acid in methanol gives the corresponding compound in which A is CO_2CH_3. The compounds of structures (II) and (III) are available commercially, or can be prepared by standard techniques.

The reaction between compounds of structure (IV) and a reagent suitable to convert the group A_b to a group A will, of course, take place under conditions which will depend on the nature of the group A_b. As already described, for example when A_b is CN, reaction with sulphuric acid under aqueous conditions affords the desired compounds of structure (I) in which A is CO_2H. Other suitable groups and conditions will be apparent to those skilled in the art. Compounds of structure (IV) are available commercially or can be prepared by standard procedures. For example, compounds of structure (IV) in which X is nitrogen, Y_b is $C(CH_2)_nCN$ and Z_b is oxygen can be prepared via the following reaction sequence:



The compounds of structure (I) and their pharmaceutically acceptable salts have been found to be PGI_2 agonists and as such are useful in therapy for the treatment of disease conditions in which such an effect is beneficial.

More specifically, the compounds are expected to have utility as antithrombotic, vasodilatory, anti-atherosclerotic, antiinflammatory and cytoprotective agents. In particular, as antithrombotic and vasodilatory agents, the compounds are expected to be useful in the treatment of cardiovascular occlusive disorders including spasmodic and thrombotic disorders; coronary heart disease (primary and secondary prevention); stroke; post-operative thrombosis utilisation including post-angioplasty; deep vein thrombosis; peripheral vascular disease and Reynaud's disease. As antiathero-sclerotic agents the compounds would be expected to reduce atherosclerotic plaque formation; and as cytoprotective agents the compounds would be expected to protect liver and gastric mucosa, protect against mucosal

and ulcerative damage and reduce infarct size in myocardial infarct.

In addition to the foregoing utilities the compounds have antihyperlipidaemic properties and as such are expected to be of use as lipid lowering agents, and in the treatment of atherosclerosis and its sequelae.

In therapeutic use, the compounds of the present invention are usually administered in a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising a compound of structure (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The compounds of structure (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

A typical suppository formulation comprises a compound of structure (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins or cocoa butter or other low melting vegetable or synthetic waxes or fats.

Preferably the composition is in unit dose form such as a tablet or capsule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the structure (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The present invention also provides a method of mimicking the effects of PGI_2 which comprises administering to a mammal in need thereof an effective amount of a compound of the structure (I) or a pharmaceutically acceptable salt thereof; and a method of treatment of cardiovascular disorders which comprises administering to a mammal in need thereof an effective amount of a compound of the structure (I) or a pharmaceutically acceptable salt thereof.

The pharmaceutically acceptable compounds of the invention will normally be administered to a subject in a daily dosage regimen. For an adult patient this may be, for example, an oral dose of between 1 mg and 500 mg, preferably between 1 mg and 250 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 25 mg, of the compound of the structure (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

The following Examples serve to illustrate the invention. Temperatures are recorded in degrees centigrade.

Examples 1 and 2

1-(7-Methoxycarbonylheptyl)-4,5-diphenyltriazole
2-(7-Methoxycarbonylheptyl)-4,5-diphenyltriazole

A solution of 8-bromooctanoic acid (8.32g) and sodium hydroxide (1.49g) in water (50ml) was added to solution of 4,5-diphenyltriazole (7.5g) (Chem. Ber., 1970, 103, 1908-17) and sodium hydroxide (1.36g) in water (75ml) and the mixture was stirred at 80°C for 21 hours. 2N Aqueous hydrochloric acid (50ml) was carefully added to the cooled reaction and then extracted with diethyl ether (3x100ml). The ether extracts were combined, washed with water (100ml), dried over anhydrous magnesium sulphate and evaporated to dryness in vacuo to give a mixture of 1(2)-(7-carboxyheptyl)-4,5-diphenyltriazole (12.2g) as an oil.

The above mixture (12.2g), p-toluene sulphonic acid, monohydrate (1.2g) and methanol (250ml) were heated at reflux through a soxhlet extractor containing 4A molecular sieves for 3.5 hours. The methanol was removed in vacuo and the residue was dissolved in dichloromethane (250ml), washed with saturated sodium hydrogen carbonate solution (200ml), water (200ml), dried over anhydrous magnesium sulphate and evaporated to dryness in vacuo. Column chromatography on silica gel eluted with dichloromethane gave 1-(7-methoxycarbonylheptyl)-4,5-diphenyltriazole (Example 1) (2.4g, 19.4%) and 2-(7-methoxycarbonylheptyl)-4,5-diphenyltriazole (Example 2) (3.2g, 25.2%) as oils.
Example 1 found: C, 72.85; H; 7.23; N, 10.93%
Example 2 found: C, 73.08, H; 7.20; N, 11.00%
$C_{23}H_{27}N_3O_2$ requires: C, 73.18; H, 7.21; N, 11.13%

Example 3

1-(7-Carboxyheptyl)-4,5-diphenyltriazole

1-(7-Methoxycarbonylheptyl)-4,5-diphenyltriazole (1g) was treated with 2N sodium hydroxide in aqueous ethanol at reflux temperature for 2.5 hours. The ethanol was removed in vacuo and the residual mixture acidified with 2N aq HCl. The aqueous solution was extracted with ethyl acetate and the organic extracts combined, dried over magnesium sulphate and evaporated to dryness in vacuo. Recrystallisation from ethanol and water gave 1-(7-carboxyheptyl)-4,5-diphenyltriazole (0.61g, 64%) as a white solid, m.p. 103-104°C.

Found: C, 72.66; H, 6.92; N, 11.44%

$C_{22}H_{25}N_3O_2$ requires: C, 72.70; H, 6.93; N, 11.56%

Example 4

2-(7-Carboxyheptyl)-4,5-diphenyltriazole

2-(7-Methoxycarbonylheptyl)-4,5-diphenyltriazole (1g) was reacted with 2N sodium hydroxide in a method similar to Example 3. Recrystallisation from ethanol and water gave 2-(7-carboxyheptyl)-4,5-diphenyltriazole (0.76g, 79%) as a white solid, m.p. 86-88°C.

Found: C, 72.70; H, 6.94; N, 11.47%

$C_{22}H_{25}N_3O_2$ requires: C, 72.70; H, 6.93; N, 11.56%

Example 5

2-(8-Carboxyoctyl)-4,5-diphenyltriazole

a) A mixture of 4,5-diphenyltriazole (11g),

1,8-dibromooctane (67.6g), and potassium carbonate (10.31g) in dry butanone (300 ml) was heated at reflux temperature for 24 hours. The mixture was filtered and the solvent evaporated to give an oily residue. Distillation to remove 1,8-dibromooctane and column chromatography on silica gel eluted with a hexane:ethyl acetate gradient gave 2-(8-bromooctyl)-4,5-diphenyl-triazole (11.13g, 54%) as an oil.
NMR δ ($CDCl_3$) 1.2-1.5 (8H, m, 4xCH_2), 1.84 (2H, m, CH_2), 2.05 (2H, m, CH_2), 3.37 (2H, t, Br-CH_2), 4.47 (2H, t, N-CH_2), 7.3-7.6 (10H, m, 2xPh) ppm

And 1-(8-bromooctyl)-4,5-diphenyltriazole (2.12g, 10.3%) as a white solid, m.p. 90-91°C after recrystallisation from hexane.
Found: C, 64.01; H, 6.47; N, 10.09; Br, 19.84%;
$C_{22}H_{26}BrN_3$ requires C, 64.08; H, 6.36; N, 10.19; Br, 19.38%
NMR δ ($CDCl_3$) 1.1-1.5 (8H, m, 4xCH_2), 1.65-1.9 (4H, m, 2xCH_2), 3.37 (2H, t, Br-CH_2), 4.20 (2H, t, NCH_2), 7.2-7.55 (10H, m, 2xPh) ppm

b) 2-(8-Bromooctyl)-4,5-diphenyltriazole (7g) in dimethylsulphoxide (220ml) was added to a suspension of sodium cyanide (1g) in dimethylsulphoxide (60ml) over 15 minutes. The reaction mixture was stirred at 24°C for 1 hour and at 50°C for 2 hours. The cooled reaction mixture was poured into water (600ml), extracted with diethyl ether (4x200ml). The extracts were combined, washed with water (100ml), dried over anhydrous magnesium sulphate and evaporated to dryness in vacuo. Column chromatography on silica gel eluted with a hexane:ethyl acetate gradient gave 2-(8-cyanooctyl)-4,5-diphenyl-triazole (5.6g, 92%) as an oil.
Found: C, 75.13; H, 7.16; N, 15.24%;
$C_{23}H_{26}N_4$ $0.5H_2O$ requires: C, 75.18; H, 7.41; N, 15.25.

c) 2-(8-Cyanooctyl)-4,5-diphenyltriazole (3.0g) was treated with sulphuric acid (50ml) and water (50ml) and the mixture heated at reflux temperature for 4 hours. Water (200ml) was added and the cooled mixture was extracted with ethyl acetate (3 x 75ml), and the organic extracts combined and evaporated to give a solid. Recrystallisation from ethanol and water gave 2-(8-carboxyoctyl)-4,5-diphenyltriazole (2.37g, 75%) as a white solid m.p. 84-85°C.
Found: C, 72.92; H, 7.20; N, 11.07%;
$C_{23}H_{27}N_3O_2$ requires: C, 73.18; H, 7.21; N, 11.13%.

Example 6

1-(8-Carboxyoctyl)-4,5-diphenyltriazole

a) 1-(8-Bromooctyl)-4,5-diphenyltriazole (ex. example 5a) (1.8g) was reacted with sodium cyanide in a method similar to Example 5b). Work-up and recrystallisation from dichloromethane and hexane gave 1-(8-cyanooctyl)-4,5-diphenyltriazole (1.16g, 74.4%) as a white solid, m.p. 77-8°C
Found: C, 77.03; H, 7.25; N, 15.35%;
$C_{23}H_{26}N_4$ requires: C, 77.06; H, 7.31; N, 15.63%.

b) 1-(8-Cyanooctyl)-4,5-diphenyltriazole (0.9g) was treated with sulphuric acid in a method similar to Example 5a. Work-up and recrystallisation from ethanol and water gave 1-(8-carboxyoctyl)-4,5-diphenyltriazole (0.58g, 64%) as a cream solid, m.p. 86-87°C.
Found: C, 73.10; H, 7.23; N, 10.82%;
$C_{23}H_{27}N_3O_2$ requires: C, 73.18, H, 7.21, N, 11.13%.

Example 7

2-(8-Ethoxycarbonyloctyl)-4,5-diphenyltriazole

A mixture of 2-(8-carboxyoctyl)-4,5-diphenyltriazole (1g), absolute alcohol (100ml) and concentrated sulphuric acid (1ml) was heated at reflux temperature for 3 hours. The solvent was removed in vacuo, the residue dissolved in diethyl ether (100ml), washed with water (50ml), dried and evaporated. The residue was chromatographed on silica gel eluted with a hexane:ethyl acetate to give 2-(8-ethoxycarbonyloctyl)-4,5-diphenyltriazole (0.81g, 76%) as an oil.
Found: C, 73.84; H, 7.78; N, 10.22%;
$C_{25}N_{31}N_3O_2$ requires: C, 74.04; H, 7.71; N, 10.36%.

Example 8

2-(6-Ethoxycarbonylhexyl)-4,5-diphenyltriazole

4,5-Diphenyltriazole (2.0g) and ethyl 7-bromo-heptanoate (1.5g) were reacted in a method similar to Example 5. Column chromatography on silica gel eluted with a hexane:ethyl acetate gradient gave 2-(6-ethoxy-carbonylhexyl)-4,5-diphenyltriazole (1.1g, 46%) as an oil.
Found: C, 73.10; H, 7.45; N, 11.11%
$C_{23}H_{27}N_3O_2$ requires C, 73.18; H, 7.21; N, 11.13%;

Example 9

2-(6-Carboxyhexyl)4,5-triphenyltriazole

2-(6-Ethoxycarbonylhexyl)-4,5-diphenyltriazole

(0.7g) was reacted with sodium hydroxide in a method similar to Example 3. Recrystallisation from ethanol and water gave 2-(6-carboxyhexyl)4,5-triphenyltriazole (0.41g, 63%) as white needles, m.p. 88-89°C.
Found: C, 71.30; H, 6.54; N, 11.73%;
$C_{21}H_{23}N_3O_3$ $0.2H_2O$ requires: C, 71.44; H, 6.68; N, 11.90%.

Example 10

2-(7-Carboxyheptyl)-4,5-diphenyloxazole

a) A mixture of benzoin (26.15g), 8-bromooctanoic acid (25.0g), 4-dimethylaminopyridine (1.35g), 1,3-dicyclohexylcarbodiimide (25.4g) and dry tetrahydrofuran (350ml) was stirred under nitrogen at room temperature for 20 hours. The reaction mixture was filtered and the filtrate was evaporated to dryness in vacuo. The residue was dissolved in dichloromethane (350ml), washed with 5% aqueous hydrochloric acid (3 x 175ml), saturated sodium hydrogen carbonate solution (2 x 200ml), saturated sodium chloride solution (220ml), dried over anhydrous magnesium sulphate and evaporated to dryness in vacuo. Column chromatography on silica gel eluted with a hexane: dichloromethane gradient gave a yellow oil. This oil was stirred in hexane to give 2-oxo-1,2-diphenylethyl 8-bromooctanoate (27.1g, 52.7%) as a pale yellow solid m.p. 60-61°C.
NMR δ ($CDCl_3$) 1.2-1.9 (10H, m, 5x CH_2), 2.46 (2H, m, $CH_2C{=}O$), 3.4 (2H,t, $BrCH_2$), 6.86 (1H, s, PhCH), 7.35-7.95 (10H, m, 2xPh) ppm.

b) A mixture of the above ester (26.8g), ammonium acetate (19.4g) and glacial acetic acid (500ml) was stirred at 80°C, under nitrogen, for 2 hours. The

glacial acetic acid was removed in vacuo and water (1000ml) was added. The aqueous was extracted with dichloromethane (3 x 250ml). The organic extracts were combined, washed with water (200ml), saturated sodium chloride solution (200ml), dried over anhydrous magnesium sulphate and evaporated to dryness in vacuo. Column chromatography on silica gel eluted with dichloromethane gave 1-(7-bromoheptyl)-4,5-diphenyloxazole (14.09g, 55%) as an oil.

NMR δ ($CDCl_3$) 1.4 (6H, m, 3x CH_2), 1.87 (4H, m, 2xCH_2), 2.85 (2H, t, N=C$\underline{CH_2}$), 3.41 (2H, t, $BrCH_2$), 7.3-7.7 (10H, m, 2xPh) ppm.

c) 2-(7-Bromoheptyl)-4,5-diphenyloxazole (13.8g) in dimethylsulphoxide (80ml) was added over 45 minutes to a mixture of sodium cyanide (1.87g) in dimethylsulphoxide (80ml). The reaction was stirred at 50°C for 2h, cooled and poured into water (500ml). The aqueous was extracted with diethyl ether (4 x 250ml). The ether extracts were combined, washed with water (250ml), dried over anhydrous magnesium sulphate and evaporated to dryness in vacuo. Column chromatography on silica gel eluted with a hexane: dichloromethane gradient gave 2-(7-cyanoheptyl)-4,5-diphenyloxazole (4.89g, 41%) as an oil.

Found: C, 80.20; H, 7.02; N, 8.13%

$C_{23}H_{24}N_2O$ requires: C, 80.31; H, 7.18; n, 8.16%;

d) 2-(7-Cyanoheptyl)-4,5-diphenyloxazole (2.5g) was reacted with sulphuric acid in a method similar to Example 5c. Recrystallisation from ethanol and water gave 2-(7-carboxyheptyl)-4,5-diphenyloxazole (1.1g, 41.7%) as a cream solid, m.p. 82-83°C.

Found: C, 76.07; H, 6.99; N, 3.79%;

$C_{23}H_{25}NO_3$ requires: C, 76.00; H, 6.93; N, 3.85%.

Examples 11 & 12

8-(3,4-Diphenylpyrazol-1-yl)octanoic acid
8-(4,5-Diphenylpyrazol-1-yl)octanoic acid

a) Formyldeoxybenzoin (10g) was suspended in ethanol (50ml) and hydrazine hydrate (5ml) added giving an orange solution which warmed to 40°C. This solution was stirred at room temperature for 3 hours and the solvent evaporated. The resulting oil was taken up in dichloromethane and washed with dilute hydrochloric acid (pH2) and water, dried over potassium carbonate and evaporated to an orange solid. This was boiled in ether, cooled and filtered giving 3,4-diphenylpyrazole (5.64g, 57%) as pale yellow crystals, m.p. 155-6°C.
NMR δ ($CDCl_3$) 7.2-7.5 (10 H, m, 2 x Ph), 7.6 (1H, s, pyraz 5-H) ppm

b) A mixture of 3,4-diphenylpyrazole (2.2g), ethyl 8-bromooctanoate (5.5g) and potassium carbonate (3.7g) in dry butanone (50ml) was heated at reflux temperature for 44 hours. The mixture was filtered and the filtrate evaporated to an oil which was chromatographed on silica gel (hexane/ethyl acetate). The oil obtained was heated at reflux temperature in a mixture of ethanol and 2N sodium hydroxide (1:1) for 1 hour. The ethanol was evaporated and the aqueous residue was acidified with dilute hydrochloric acid to pH 3, extracted with dichloromethane, dried over magnesium sulphate and evaporated to a solid. This was recrystallised from dichloromethane/ether to give 8-(3,4-diphenylpyrazol-1-yl)octanoic acid (0.48g, 13%) as colourless crystals, m.p. 114-5°C.
Found: C, 76.02; H, 7.25; N, 7.63%
$C_{23}H_{26}N_2O_2$ requires: C, 76.21; H, 7.23; N. 7.73%

c) The mother liquor from above was evaporated to an oil which was chromatographed on silica gel (dichloromethane/methanol) giving a solid which was recrystallised from ether/petroleum ether to give 8-(4,5-diphenylpyrazol-1-yl)octanoic acid (0.15g, 5%) as colourless crystals, m.p. 94-5°C.

Found: C, 76.53; H, 7.26; N, 7.82%

$C_{23}H_{26}N_2O_2$ requires: C, 76.21; H, 7.23; N, 7.73%

BIOLOGICAL DATA

METHOD FOR MEASUREMENT OF AGGREGATION OF WASHED HUMAN PLATELETS

Platelets were prepared from freshly drawn human blood. Blood was collected into acid citrate anticoagulant, centrifuged (5 min at 500g), and the upper layer of platelet-rich plasma was removed. This platelet-rich plasma was incubated with aspirin (100μM) for 10 min at 37°C and then centrifuged (15 min at 200g). The platelet pellet was resuspended (at approx. 1.5×10^8 cells/ml) in medium containing NaCl (145mM), KCl (5mM), $MgCl_2$ (1mM), $CaCl_2$ (0.2mM), Hepes (10mM, pH 7.4 at 37°C), glucose (10mM), apyrase (10μg/ml). Aggregation was monitored (as a change in optical density) at 37°C in a 4 channel aggregometer (PAP-4 from Biodata Corp.). Fibrinogen (1mg/ml) and $CaCl_2$ (1mM) were added to aliquots of platelets that were continuously stirred. The test compound (or 0.1% DMSO vehicle) was added 2 min before the aggregatory stimulus (1μM U46619). The extent of aggregation was assessed 4 min after addition of the stimulus, and was calculated as % of the control response in the absence of test compound. Dose-response curves were constructed for measurement of IC_{50} values for each compound.

METHOD FOR MEASUREMENT OF K_I FOR INHIBITION OF [^{3}H]ILOPROST BINDING TO HUMAN PLATELET MEMBRANES

Membranes were prepared from outdated platelet-rich plasma concentrates obtained from the Blood Transfusion Service. The platelets were homogenised in buffer containing Tris-Cl (5mM, pH 7.4 at 20°C) and EDTA

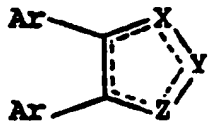
(0.25mM), and then centrifuged (10 min at 26,000g). The membrane pellet was washed twice by homogenisation in buffer containing Tris-Cl (50mM, pH 7.4 at 20°C) and EDTA (0.25 mM), followed by centrifugation. For measurement of [^{3}H]iloprost binding, membranes (0.4-0.8mg) were incubated in the presence of Tris-Cl (50mM, pH 7.4 at 20°C), $MgCl_2$ (4mM), EDTA (40μM), [^{3}H]iloprost (10nM), DMSO (1.85%), and varying concentrations of the test compounds. For determination of non-specific binding, 20μM iloprost was included. The tubes (triplicates for each condition) were set up on ice, and then incubated for 30 min at 37°C. The incubations were terminated by rapid filtration on Whatman GF/B filters using a Brandel Harvester. The filters were washed and then counted for radioactivity. The K_i of the test compounds for inhibition of binding of [^{3}H]iloprost to human platelet membranes was calculated from the IC_{50} for displacement of [^{3}H]iloprost binding.

RESULTS

The compounds of the Examples in general had IC_{50} (aggregation) values in the range of from 0.01 - 2.3μM; and Ki(μM) values in the range of from 0.8 - 10μM.

Claims:

1. A compound of structure (I):



(I)

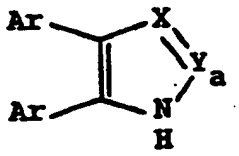
in which
each group Ar is the same or different and is optionally substituted phenyl or optionally substituted heteroaryl;
X is nitrogen or CR^1
Y is nitrogen, $N(CH_2)_nA$ or $C(CH_2)_nA$
Z is nitrogen, oxygen or $N(CH_2)_nA$, and the dotted line indicates the optional presence of a double bond so as to form a fully unsaturated heterocyclic ring;
R^1 is hydrogen, C_{1-4}alkyl, optionally substituted phenyl or optionally substituted heteroaryl;
n is 4 to 12; and
A is CO_2H or a group hydrolysable to CO_2H, 5-tetrazolyl, SO_3H, $P(O)(OR)_2$, $P(O)(OH)_2$, or $P(O)(R)(OR)$ in which R is hydrogen or C_{1-4}alkyl,
or a pharmaceutically acceptable salt thereof,
provided that

- X, Y and Z are not all at the same time, nitrogen;
- when X is CR^1, Y and Z are not both nitrogen;
- when Y is $N(CH_2)_nA$, Z is nitrogen; and
- when Z is oxygen, Y is $C(CH_2)_nA$.

2. A compound according to claim 1 in which each group Ar is phenyl, X and Z are both nitrogen and Y is $N(CH_2)_nX$ in which n is 8 and X is CO_2R in which R is C_{1-4}alkyl.

3. A process for preparing a compound according to claim 1 which comprises:

(a) for compounds in which Z is other than oxygen reaction of a compound of structure (II):



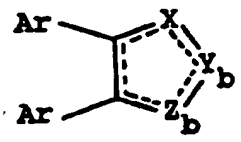
(II)

in which
Ar and X are as described in structure (I) and Y_a is N or $C(CH_2)_nA$; with a compound of structure:

$$L(CH_2)_nA \qquad (III)$$

in which n and A are as described for structure (I) and L is a leaving group; or

(b) reaction of a compound of structure (IV):



(IV)

in which Ar and X are as described in structure (I), Y_b is N, $N(CH_2)_nA_b$ or $C(CH_2)_nA_b$, Z_b is N, O or $N(CH_2)_nA_b$ provided that:

- X, Y_b and Z_b are not all nitrogen,
- when X is CR^1, Y_b and Z_b are not both nitrogen,
- when Y_b is $N(CH_2)_nA_b$, Z_b is nitrogen, and
- when Z_b is O, Y_b is $-C(CH_2)_nA_b$;

A_b is a group convertible to a group A as described in structure (I), with a reagent suitable to convert the group A_b into a group A and, optionally thereafter, converting one group A into another group A, and optionally forming a salt.

5. A pharmaceutical composition comprising a compound according to claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutical carrier.

6. A compound according to claim 1 for use in therapy.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/01545

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 D 249/04, 231/12, 263/32, A 61 K 31/41

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	FR, A, 2104651 (ROBERT ARIES) 21 April 1972, see the whole document	1-6
X	FR, A, 2082166 (ROBERT ARIES) 10 December 1971, see the whole document	1-6
X	GB, A, 1206403 (JOHN WYETH & BROTHER LIMITED) 23 September 1970, see the whole document	1-6
X	US, A, 3948932 (ROBERT THOMAS BUCKLER ET AL.) 6 April 1976, see the whole document	1-6

* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
18th December 1991	- 9. 01. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	M. PEIS M. Peis

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/GB 91/01545

SA 51137

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 31/10/91
The European Patent office is in no way liable for theseparticulars which are merely given for the purpose of information.

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FR-A- 2082166	10/12/71	NONE		
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